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REMARKS

Claims 1 through 32 are pending. No claims are amended, and no new claims have been added.

Applicants thank the Examiner for her acknowledgements and entry of the preliminary amendment filed July 23, 2002, the election of Group I, claims 1-32, and the Rule 1.47(a) status of the application.

Objections to Specification

Applicants acknowledge the Examiner's objections to informalities in the disclosure and thank her for the suggested changes to overcome the objections. The disclosure is amended by this response to include those changes, and Applicants respectfully request that the objections be withdrawn in light of the amendments.

Rejection of claims 1-32 under 35 U.S.C. §103

The Examiner rejected claims 1-2, 5-6, 9-10, 13-14, 17-18, 21-22, 25-26, and 29-30 under 35 U.S.C. §103(a) as being obvious over Kohroki et al., Biochemical and Biophysical Research Communications, vol. 262, pages 365-367, August 1996 ("Kohroki") in view of Loewy (U.S. Patent No. 5,914,229) ("Loewy"). The Examiner also 3-4, 7-8, 11-12, 15-16, 19-20, 23-24, 27-28, and 31-32 under 35 U.S.C. §103(a) as being obvious over Kohroki in view of Loewy and further in view of Weinstein (U.S. Patent 6,270,966) ("Weinstein"). Applicants respectfully traverse the rejections and request that claims 1-32 be allowed as written.

"To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)." M.P.E.P. § 2143.03. MPEP section 2143 sets forth the basic requirements for the patent and trademark office to establish *prima facie* obviousness as follows: "to establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine

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reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

A case of obviousness requires that there be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. See MPEP § 2143; *In re Linter*, 458 F.2d 1013, 173 USPQ 560, 562 (CCPA 1972). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990), *W.L. Gore and Associates, Inc. v. Garlock, Inc.* 220 USPQ 303 (CAFC, 1966). Moreover, the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

Without waiver of or prejudice to any other arguments in support of the patentability of the claimed invention, applicants respectfully submit that the Office Action fails to meet the burden of showing *prima facie* obviousness of the claimed invention at least for the reason that the combination of references does not teach or suggest all the claim limitations.

The Office Action states in part that "Kohroki et al teach a method for the identification and characterization of gene expression in one or more samples, comprising: ...providing an identimer comprising an oligo-dT primer sequence from 5' 3' end wherein said identimer also comprises a detectable marker at one end; ..." Assuming for purposes of argument only that the oligo-dT of Kohroki is an "identimer," Kohroki discloses only "mixed oligo dT primers (5'-GCGAGTCGACCG(T)14VN-3', where V are G, A, and C, and N are G, A, T, and C)..." (Page 365, "Materials and Methods," first full paragraph.) Thus, Kohroki discloses only an oligo-dT augmented with a "VN" nucleotide grouping at the 3' end, and the oligo-dT primers of Kohroki provide only 12 combinations of a "VN." After its reverse transcription, second strand synthesis, and digestion steps, Kohroki further requires

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ligation of the 3' end cDNA fragments to an adapter, AEP, to further devolve the samples under study.

Unlike Kohroki, the present invention, as claimed in all pending independent claims 1, 5, 9, 13, 17, 21, 25, and 29, and their respective dependent claims, contain the claim limitation of an identifier of at least Tn-VNNN, typically TnVN_x, where x is an integer 3 or greater but not more than 10. For example, Claim 1, element (b), claims the step of:

"providing an identifier comprising an oligo-dT primer of sequence, from 5' to 3' end, of Tn-VN_x, where n is an integer 8 or greater but not more than 50 representing the number of T's, V equals a nucleotide A, C, or G but not T, each N equals a nucleotide A, C, G, or T, and x is an integer 3 or greater but not more than 10 representing the number of N nucleotides, said identifier also comprising a detectable marker at its 5' end;" (emphasis added)

Thus, the present invention comprises an oligo-dT primer of sequence, from 5' to 3' end of either VNNN or VN_x, where each N equals a nucleotide A, C, G, or T, and x is an integer 3 or greater but not more than 10 representing the number of N nucleotides. Thus, by design, the claimed invention may support high-throughput analysis and provide sufficient sequence information to allow for gene prediction against a genomic database (derived from the VNNN, VN_x, restriction site, and fragment length).

Kohroki does not teach the VNNN or VN_x limitation of the present invention which by itself permits a combination of at least 192 or more permutations. Indeed, Kohroki would not provide sufficient information to support gene prediction and also would not be amenable to high-throughput processing (e.g. HPLC analysis), unlike the present invention. Because any combination of the cited references including Kohroki would not teach or suggest the Tn-VNNN or Tn-VN_x limitation of the present invention, the Office Action fails to demonstrate a prima facie case of obviousness. Therefore Applicants respectfully request that the rejection of Claims 1-32 based on any combination of references be withdrawn.

The deficiencies of any combination of references with Kohroki are not cured by combination of Kohroki with Loewy. The Office Action admits that Kohroki does not teach wherein the adapter comprises an RNA polymerase promoter site or wherein the amplifying one or more ligated cleavage fragments occurs by means of *in vitro*

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transcription using one or more RNA polymerases to produce *in vitro* transcribed RNA. The Office Action attempts to cure this deficit by combination with Loewy. However, as discussed below, Applicants respectfully traverse all rejections based in whole or in part on the combination of Kohroki and Loewy.

Assuming for purposes of argument only that Loewy teaches utilization of adapters comprising an RNA polymerase promoter site, as described in the Office Action, Applicants respectfully disagree that one of ordinary skill in the art would be motivated to combine Kohroki and Loewy because the references teach away from any such combination.

"A reference may be said to teach away ... if ... the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Tec Air Inc. v. Denso Manufacturing Michigan, Inc.*, 52 USPQ2d, 1294 (Fed. Cir. 1999). Applicants submits that Kohroki with the assumed features of Loewy could not result in the claimed invention.

Instead, the final step of Kohroki involves the ligation of an adapter to double-stranded DNA fragments that have been digested with the restriction enzyme (Sau3A I). From this ligated adapter, Kohroki amplifies the cDNA fragments using combinations of the TEP and AEP primers. Although the Office Action states that the incorporation of an RNA polymerase site into the adapter described by Kohroki would be obvious to anyone skilled in the art, the use of an RNA polymerase (*in-vitro* transcription) and the use of the AEP PCR primers are exclusive. That is, the amplification of the cDNA fragment using an RNA polymerase requires a specific promoter site/sequence (T3 or T7) that is not amenable to the addition of variable nucleotide groups ("NN") of the AEP of Kohroki. RNA polymerase typically binds to the promoter site/sequence and begins synthesizing (transcribing) complementary cRNA at the promoter site; the addition of the NN bases on a T3 or T7 promoter sequence would have no impact on the subsequent sequence that is amplified, or possibly act to decrease or inhibit RNA polymerase activity. Thus, in the case of Kohroki, the utilization of an RNA polymerase promoter site/sequence would result in the amplification of all cDNA fragments ligated to the adapter, and one would still have 12 subsets derived in the first step using the TEP primer. In contrast, the utility of the TEP or AEP primers requires a DNA polymerase, such as those used in PCR and reverse transcription, to allow the variable

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groupings (e.g. VN) to facilitate the amplification of complementary sequences while simultaneously prohibiting the amplification of non-complementary sequences. Thus, the methods and compositions of Kohroki teach away from any combination with Loewy, and the Office Action fails to state a prima facie case of obviousness. Accordingly, Applicants respectfully request that this rejection be withdrawn.

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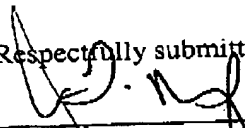
CONCLUSION

For at least these reasons, Applicants respectfully urge that the application is now in condition for allowance. It is believed that any additional fees due with respect to this paper have already been identified in any transmittal accompanying this paper.

However, if any additional fees are required in connection with the filing of this paper that are not identified in any accompanying transmittal, permission is given to charge deposit account number 18-0013 under Order No. 65446-0087, in the name of Rader, Fishman and Grauer PLLC. If the Examiner has any questions or comments, she is kindly urged to call the undersigned to facilitate prosecution.

Respectfully submitted,

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